Questions

losartan
January 6, 2003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Cardio-Renal Advisory Committee is asked to opine on the relative effects of an antihypertensive regimen containing losartan compared with a regimen containing atenolol, both administered once per day. Specific guidance is sought on the adequacy of the current program to support a claim of superior efficacy for losartan at reducing the incidence of the combined endpoints of cardiovascular mortality, MI and stroke, as well as guidance on how to describe any relevant differences in labeling. Additionally, guidance is sought regarding the relevance and appropriate description for an observed qualitative interaction between race and the effects of the two study drugs.

In the past, the Agency has told sponsors that a robust demonstration of a clinically relevant difference between two drugs, if done fairly, would be appropriate for inclusion in labeling. There are few examples of such trials being presented to the Agency and being incorporated into labeling, such that the current trial has some value as precedent.

1. The LIFE trial compares the effects of losartan and atenolol on cardiovascular outcomes. For a population like that studied in LIFE, what is known from external sources about the effects of beta-blockers (including atenolol) and angiotensin receptor blockers (ARBs) (including losartan) on the incidence of death, MI or stroke? Describe the basis for your position.
   1.1. Cannot be determined.
   1.2. Both are superior to placebo and equivalent to each other.
   1.3. One or both are superior to placebo, but not equivalent to each other (specify ranking).
   1.4. Both are equivalent to placebo.
2. Regarding the LIFE trial data in the overall population studied, describe the overall difference between patients receiving the losartan-based regimen and the atenolol-based regimen in the trial.
   2.1. Was superiority of the losartan-based regimen demonstrated:
      2.1.1. for the primary endpoint?
      2.1.2. each of the three components of the primary endpoint?
   2.2. Was the comparison between the two regimens a fair one, as discussed in the ICH E10 Guidance? For example, were appropriate doses of both medications used?
   2.3. Could the observed differences in clinical outcomes be the result of differences in blood pressure control? Recall that the two

groups had 'similar' but not identical reductions in blood pressure measured at trough, but that limited data are available to compare blood pressures at other time points.

3. Are the results of LIFE alone an adequate basis for approval of losartan to reduce the combination of cardiovascular mortality, MI and stroke?
4. If not, are the results of LIFE, combined with prior expectations derived from the other sources you considered in question one an adequate basis for approval of losartan to reduce the combination of cardiovascular mortality, MI and stroke?
5. Do you recommend approval of losartan as having demonstrated superior efficacy when compared with atenolol in the population studied in LIFE to reduce the incidence of the combination of cardiovascular mortality, MI and stroke? If so, how should the FDA think about describing this trial (and others like it) in labeling?
   - 5.1. Narrowly, as comparisons between two drugs of different classes in a specific population of hypertensive patients, to be described as extensions of antihypertensive efficacy?
   - 5.2. More broadly, as comparisons between drugs of different classes in individuals identified as being 'high-risk', to be described as novel indications? If so, how should the findings of these trials be included in the approved labeling for losartan?
     - 5.2.1. As demonstrating superiority of losartan over atenolol in the population?
     - 5.2.2. As demonstrating superiority of losartan over placebo in the population?
6. The sponsor has presented analyses looking at the comparative effects of the two drugs in a number of demographic subgroups. None of these analyses were allocated alpha as part of the statistical plan. Do any of these analyses meet the standard for robustness of clinical data sufficient to support the description of the effects of losartan in the population? If so, please identify that population or populations and the basis for your conclusion.
   - 6.1. Patients with left ventricular hypertrophy identified by ECG criteria
   - 6.2. Women
   - 6.3. Patients with isolated systolic hypertension
   - 6.4. Patients with diabetes
7. The FDA has identified an association between atenolol use, atrial fibrillation and stroke. Does this analysis, combined with other available data meet the standard for robustness of clinical data sufficient to support a description of these effects? If so, where?
8. You have heard a discussion of qualitative and quantitative interactions among subgroups. For one relevant subgroup, African-Americans in the U.S., atenolol is apparently superior to losartan in its effects on the primary endpoint. No biologic rationale for this

apparent qualitative interaction with race has been identified by the FDA or the sponsor.

8.1. Does the lack of this rationale matter to you?

8.2. Are there other data you feel illuminate the observed differences? Do you find this outcome surprising?

8.3. Do you find the difference compelling? If so, which of the following describe the relationship of losartan (L), atenolol (A), and an imputed placebo (IP) with regard to their effects on the primary endpoint in African-Americans:

- 8.3.1. A>L>IP?
- 8.3.2. A>L=IP?
- 8.3.3. A>IP>L?
- 8.3.4. Other ordering?
- 8.3.5. Cannot tell?

8.4. How should the finding be described in labeling? Please provide specific language if possible.

- 8.4.1. Contraindication to the use of losartan in African-Americans if the goal is the reduction in death etc.?
- 8.4.2. Warning or Precaution that this interaction exists.
- 8.4.3. Description in the Clinical Trials section.
- 8.4.4. No description of this finding in labeling.